

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ



Armed Forces College of Medicine

AFCM



Treatment of Angina

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Cardiopulmonary module



Lecture 1:

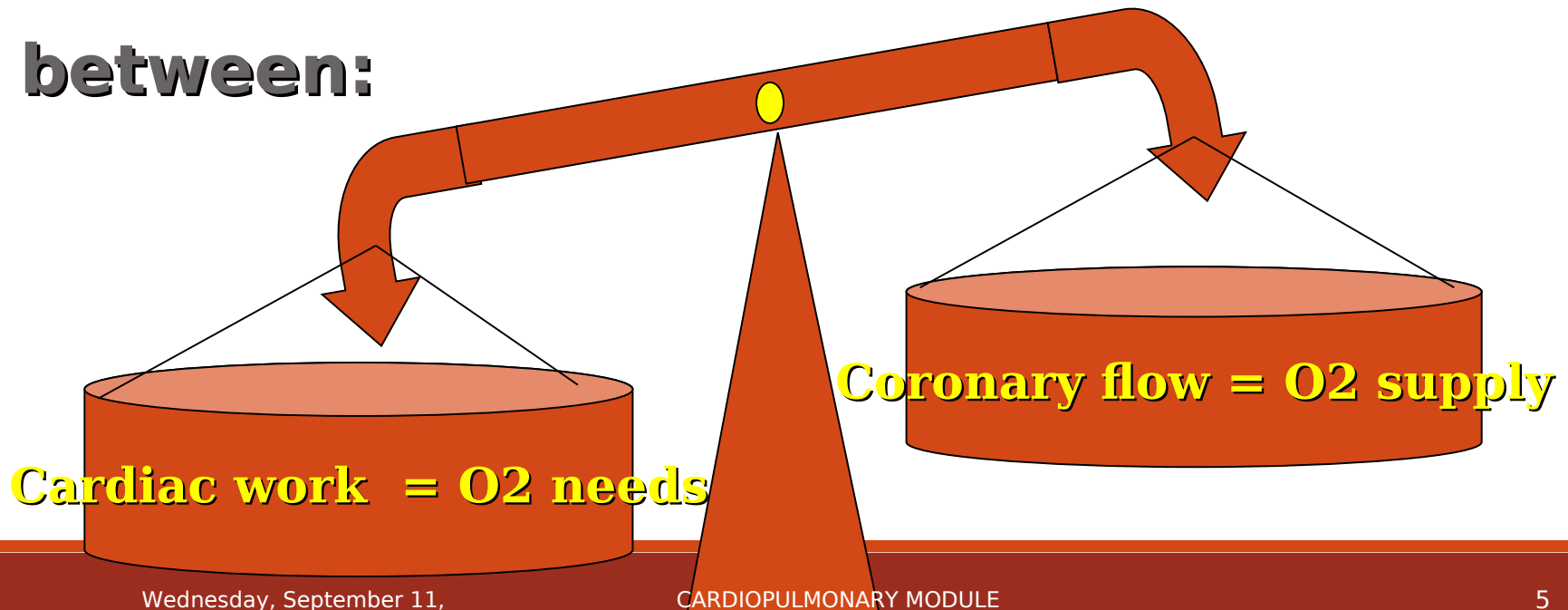
- 1) Classify the groups of antianginal drugs according to their mechanisms of action
- 2) Identify the role of nitrates in the treatment of angina
- 3) Explain the adverse effects, precautions and drug preparations of nitrates,



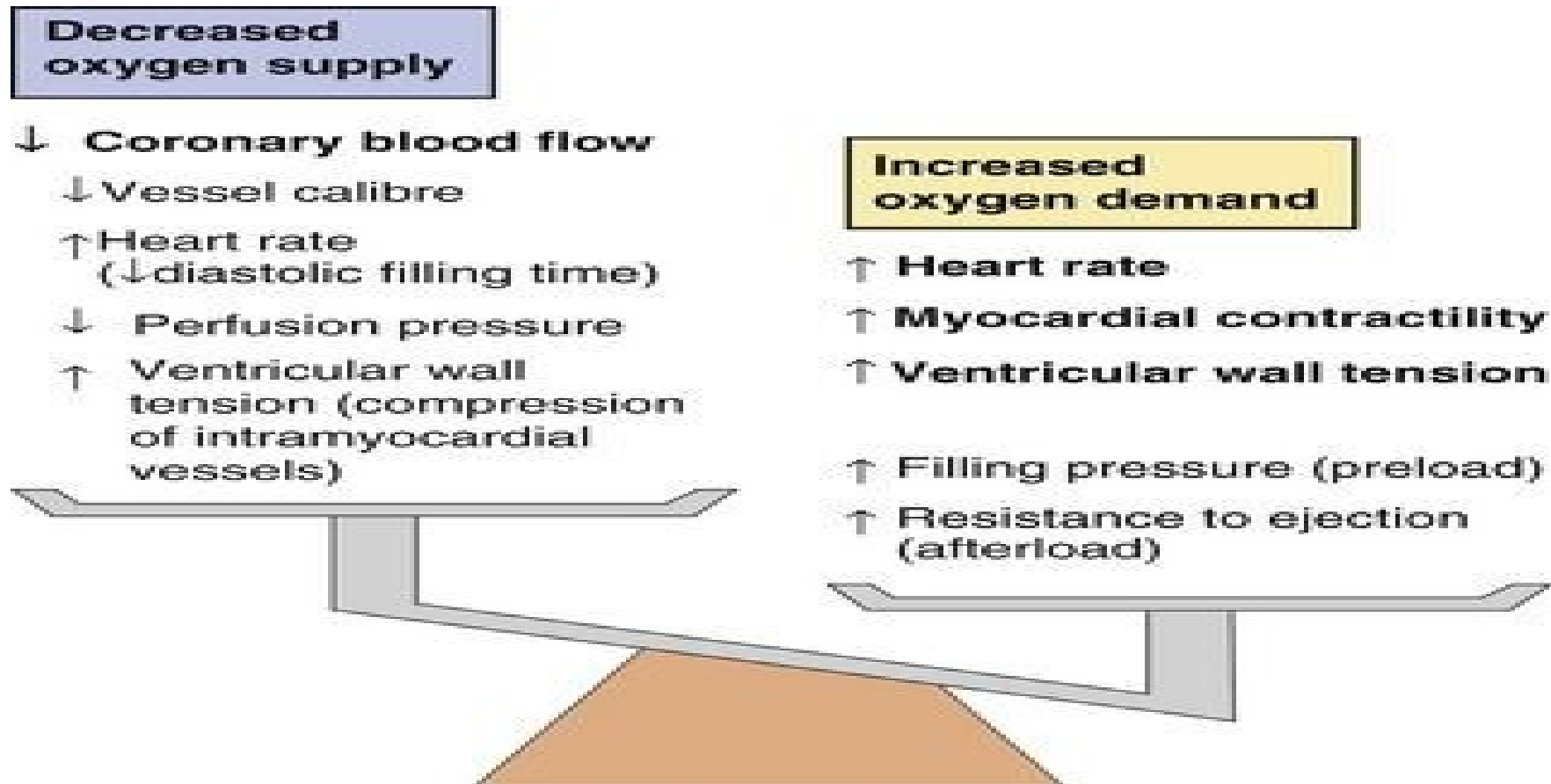
Angina Pectoris

Definition Chest pain due to transient myocardial ischemia.

Cardiac ischemia is due to **imbalance** between:



Determinants of Myocardial Oxygen Demand



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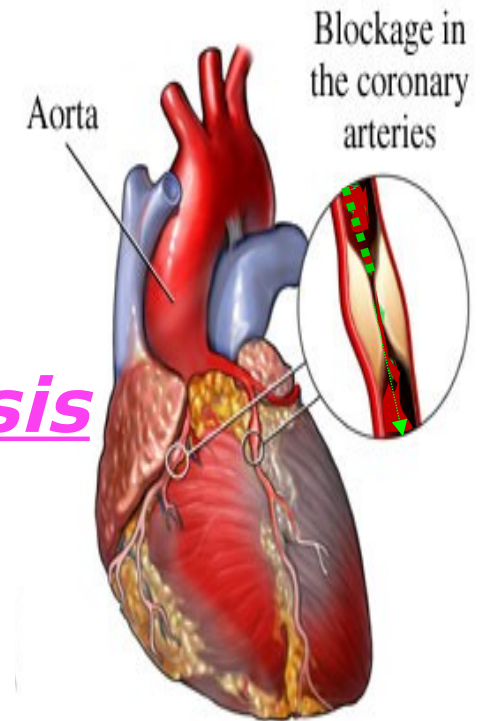


Angina Pectoris

Types of Angina

1- Angina of Effort (Exertional, Stable, Classic):

- Most common type. Occurs on exertion and relieved by rest.
- Due to coronary atherosclerosis. Coronary lumen is narrowed & fixed.
- Treatment by ~~coronary~~ **Cardiac work.**

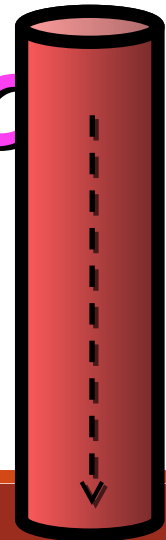




Angina Pectoris

2- Variant (Prinzmetal, Vaso-spastic) Angina:

- a- Occurs at rest, usually accompanied by arrhythmia.
- b- Due to *reversible coronary V.C*
Supersensitive coronary.
- c- Treatment by *Coronary V.D.*





Angina Pectoris

3- Unstable Angina (Pre-infarction, Crescendo):

⚡- Emergency case ▮

a- Progressive worsening → Occurs on exertion then on rest.

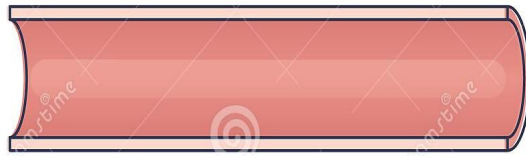


b- Progressive *occlusion* of coronary on top of atherosclerosis.



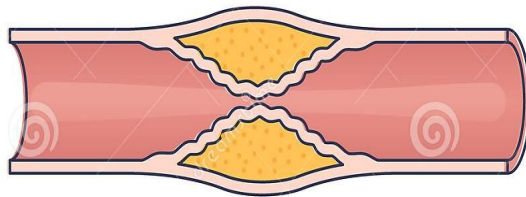
c- ~~Treatment:~~ **Coronary V.D.** **Hospitalization** → **+** **↓ Cardiac work**
+ Anti-thrombotics

NORMAL



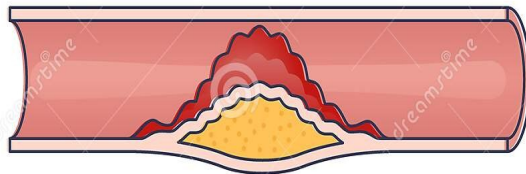
Normal Coronary Artery

STABLE ANGINA



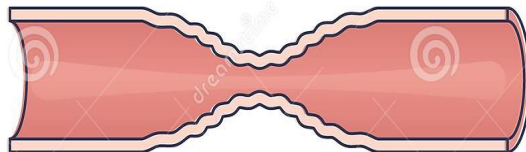
Atherosclerosis

UNSTABLE ANGINA

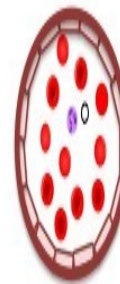


Atherosclerosis with Blood Clot

VARIANT ANGINA



Coronary Spasm



Normal

Atherosclerotic plaque



Exertional Angina



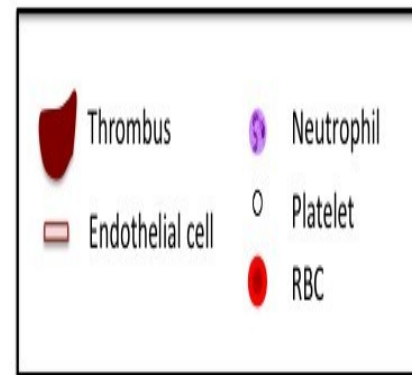
Vasospastic Angina



Unstable Angina



Infarct



Management Of Angina Pectoris

I- General Measures

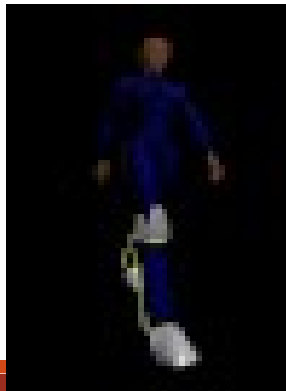
1- Change life

style :

Stop smoking

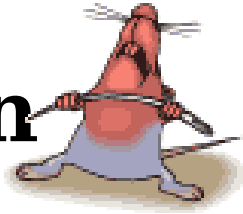
Gradual exercise

Weight reduction



2- Avoid :

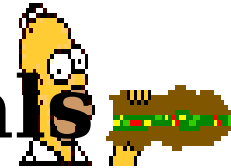
Exertion



Emotions

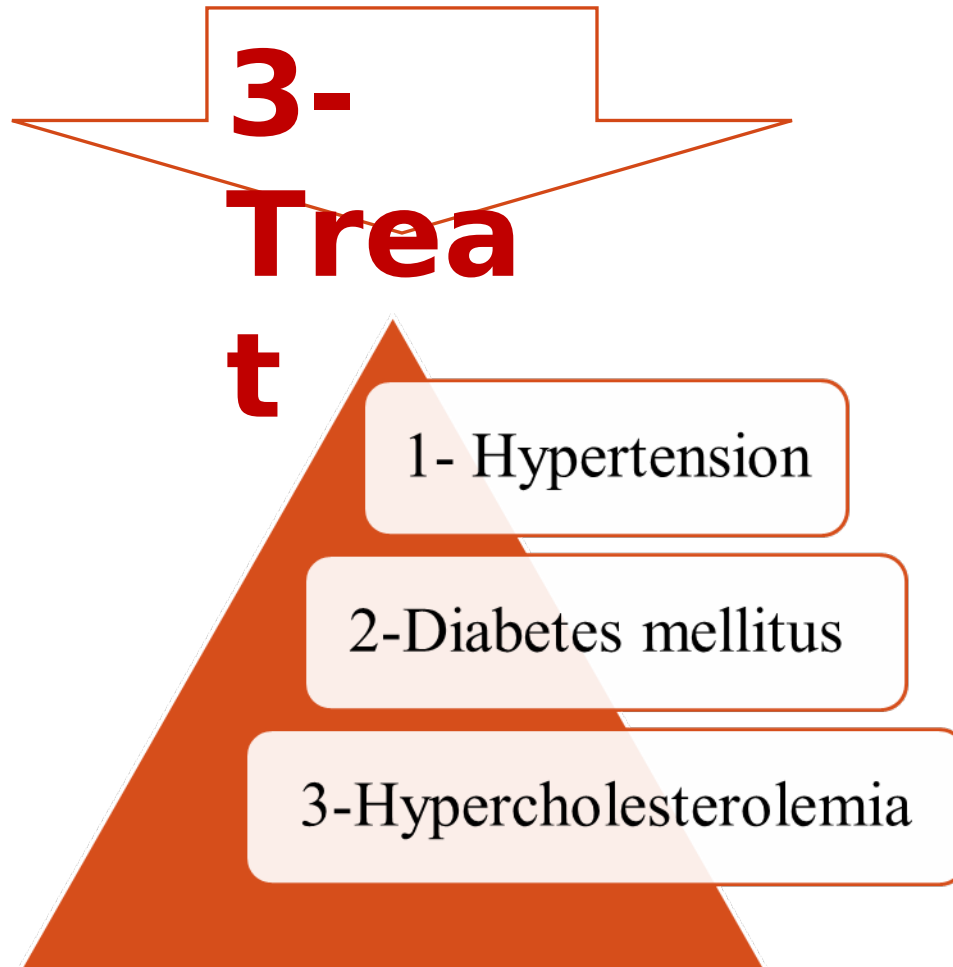


Eating heavy fatty meals



Exposure to cold.





II-Drug Treatment of Angina



A) Anti-Anginal Drugs:

1-Nitrates

2- Calcium Channel Blockers

3- β -Blockers

4- Other drugs

- a- Nicorandil
- b- Trimetazidine
- C- Ranolazine
- D- Ivabradine

B) Adjuvant Drugs:

1- Anti-Platelet:

Aspirin, clopidogrel, Dipyridamol & Ticlopidine

2- Drug treatment of Risk & Precipitating factors e.g. Anti-anxiety, Antihypertensive, Anti-hyperlipidemic, Anti-diabetic, etc



1- Nitrates

Organic nitrates

a- Glyceryl Trinitrate (GTN, Nitroglycerin).

b- Isosorbid

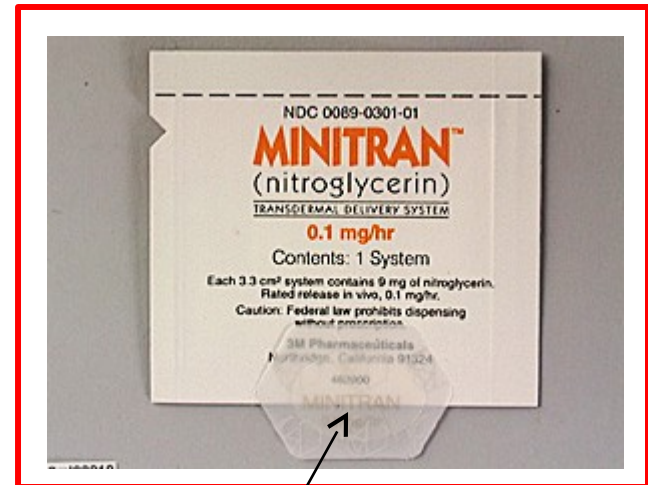
Dinitrate.

C- Isosorbid
Mononitrate.



Pharmacokinetics:

1- Absorbed from Buccal & Intestinal mucosa, and skin.





Drug Treatment of angina

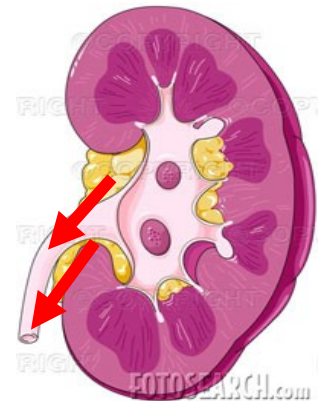
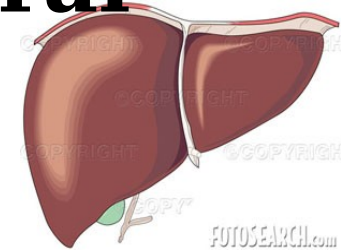
2- Extensive hepatic first pass metabolism (90 %) → 10 % Oral bioavailability.

Isosorbide dinitrate is converted into isosorbide 5-mononitrate (active metabolite)

• All except isosorbide mononitrate undergo extensive and variable first pass metabolism in liver (90 %).

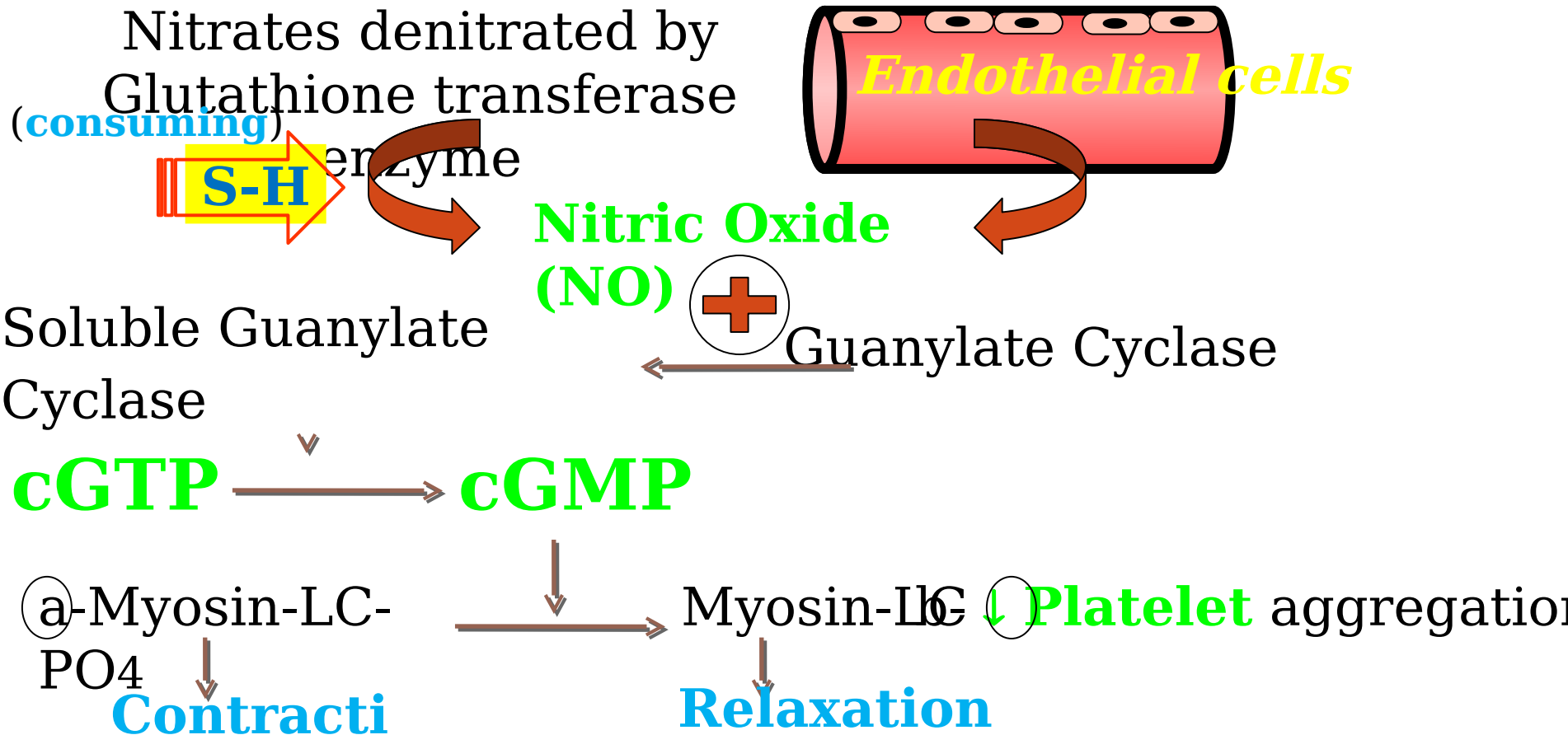
3- Excreted as Glucuronide conjugates

• 10 % Oral bioavailability (so used as Sustained release tab (SR))





Pharmacodynamics





Pharmacological Actions of Nitrates:

1- Blood Vessels

2- Heart

3- Blood pressure

4- Smooth muscle

1- Blood Vessels

a- V.D. of Normal, mainly Big vessels, Veins

Veins express greater amount of the enzyme that generates NO from GTN than arteries

- Powerful Veno-V.D. → ↓ V.R. → ↓ E.D.V. →

① ↓ Pre-Load.

② ↓ Pulmonary vascular pressure and heart size

③ ↓ C.O.P. → ↓ Systolic B.P. mainly.

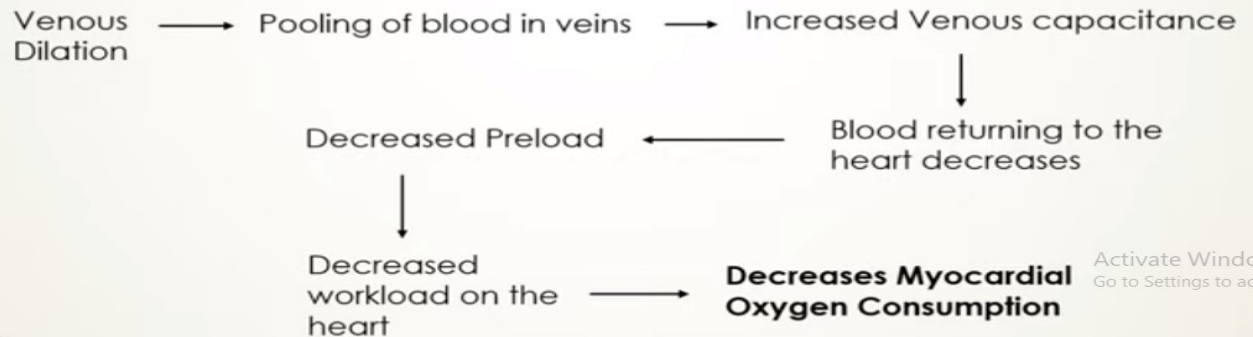
b- Some Arterio-

→ ↓ T.P.R. →

① ↓ After-load.

② ↓ Diastolic B.P.

• Less Arteriodilation (Coronary Arteries)





1- Blood Vessels

**c- V.D. of big epicardial normal coronaries →
Redistribution to ischemic area.**

d- Meningeal V.D.: Headache

**e- Cutaneous V.D. : Flush of face and chest
(Nitroid reaction)**

**f- Pulmonary V.D.: decreasing VR, decreasing
Pulmonary pressure**

2- Heart

♥ a - Decrease Cardiac work (\downarrow Preload $>$ \downarrow Afterload) & \downarrow Oxygen consumption.

♥ b - Powerful Veno-Dilator $\rightarrow \downarrow$ V.R. $\rightarrow \downarrow$ E.D.V. \rightarrow
- \downarrow Pre-load
- \downarrow Contractility $\rightarrow \downarrow$ Pressure on Sub-endocardial coronaries.

♥ c - Some Arterio-V.D. $\rightarrow \downarrow$ T.P.R. $\rightarrow \downarrow$

3-Blood pressure

Hypotension: \downarrow S.Bl.p. $>$ D.Bl.p.

- Hypotension \rightarrow

Reflex \uparrow

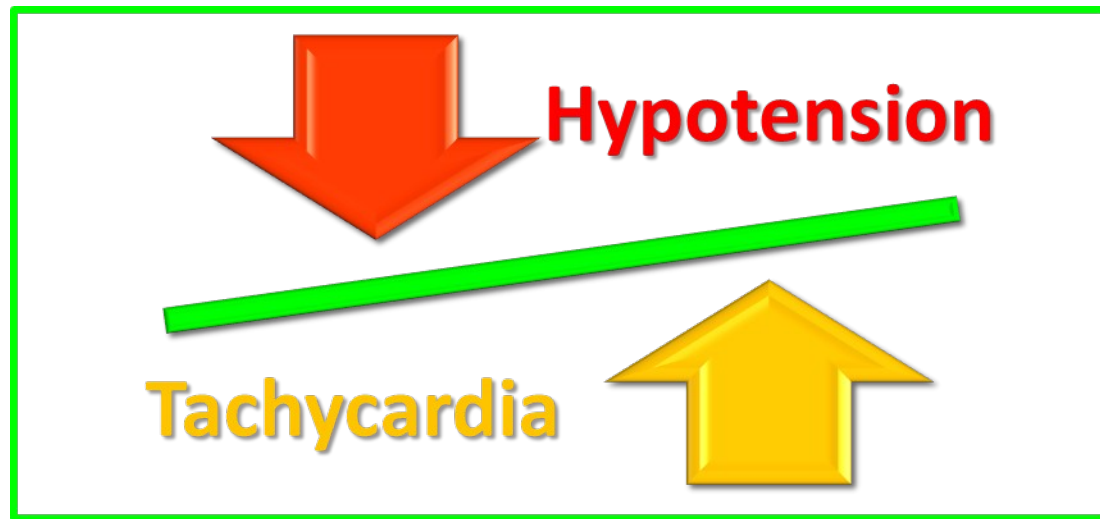
Sympathetic $\rightarrow \uparrow$

Contractility

& Tachycardia \rightarrow

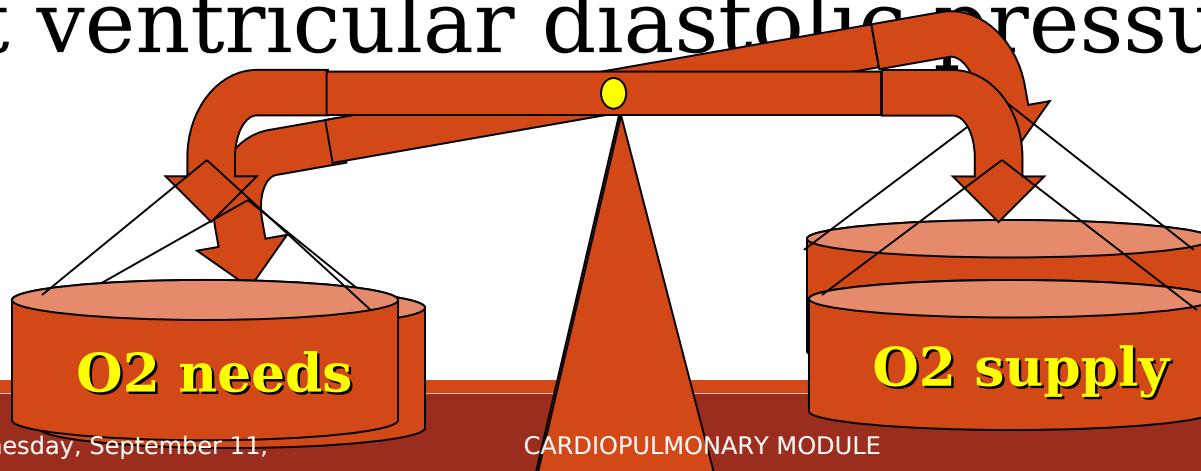
This effect could be antagonized by:
beta-Blockers or Verapamil (CCB).

Coronary Perfusion



So the beneficial effects of nitrate are:

- [- Decreased O₂ requirement due to decreased B.P., decreased ventricular volume and ejection time.
- [- Increased O₂ supply by dilating epicardial coronary vessels and increased collateral flow and decreased left ventricular diastolic pressure.



4-Smooth muscle and R.C.

- Spasmolytic on smooth muscles of **Bronchial, biliary, GIT, Urinary bladder & Uterus.**
- **Reflex stimulation of R.C.: Stimulation of Chemo- and Baro-receptors**

Preparations & Doses of Nitrates:

Preparations of Nitrates

- **Short acting:** Used in acute attack (*may be repeated every 5 min till pain disappears or maximum 3 doses*) and immediate prophylaxis (*taken 5 minutes before effort*).

- a. Glyceryl Trinitrate (GTN, Nitroglycerin).
- b. Isosorbide Dinitrate

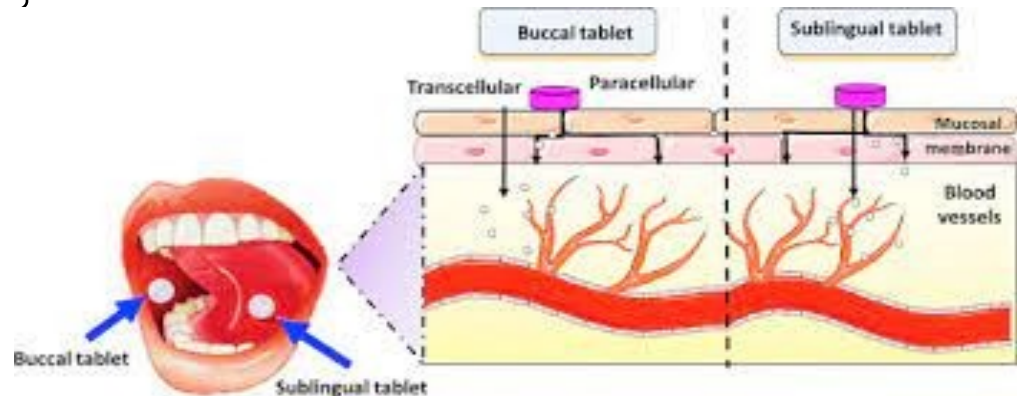
} **S.L or buccal spray**

If side effects appear either:

Spit or swallow the pellet

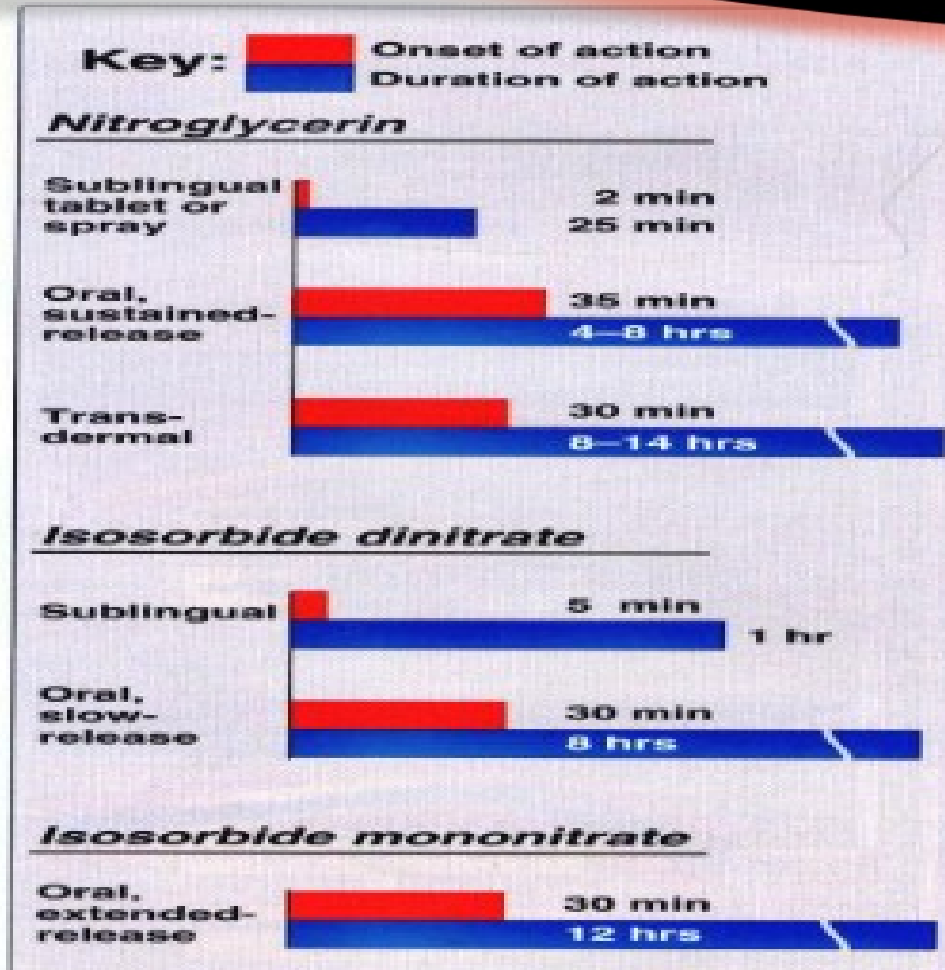
- **Long acting:** Used in prophylaxis of all types of angina

- a. Glyceryl Trinitrate (GTN, Nitroglycerin).
(SR tablets, Transdermal Delivery System TDDS (patch or ointment).)
- b. Isosorbide Dinitrate (Tablets, chewable tablets & SR capsules)
- c. Isosorbide Mononitrate. (Tablets & SR capsules)



Nitroglycerin is available as an intravenous solution used chiefly to reduce preload and afterload in patients who have acute heart failure associated with MI and hypertensive crisis.

Preparations & Doses of Nitrates:



Therapeutic Uses of Nitrates

1- All Types of Angina

Pectoris:

1- Angina of effort: decreasing cardiac work (preload more than after load) and oxygen consumption.

2- Variant Angina: coronary V.D.

3- Unstable Angina → decreasing cardiac work (preload more than after load) + oxygen consumption + coronary V.D.

Therapeutic Uses of Nitrates

1- All Types of Angina

Pectoris:

① **Acute attacks** : nitroglycerin or isosorbide dinitrate sublingual or oral spray.

✱ Repeat the drug every 5 min. till disappearance of pain or maximum 3 doses, otherwise → Acute Myocardial Infarction.

In Immediate Prophylaxis → Drugs are taken 5 minutes before exertion.

② **In Long Term Prophylaxis** → Long Acting

Nitrates: Oral S.R. (Large dose to overcome Hepatic First Pass Effect), Trans-dermal patch or Ointment →

Slow release Oral preparations

Therapeutic Uses of Nitrates

2- Nitroglycerin IV infusion

a-Acute myocardial infarction (A.M.I.), Acute Pulmonary Edema (Acute Left Ventricular Failure) & Refractory **H.F.** → ↓ coronary resistance, ↓ oxygen consumption, ↓ Pulmonary congestion & may ↓ the size of infarcted area.

b-Controlled hypotension during noncardiac

3- Congestive heart failure with high preload to ↓ pulmonary congestion.

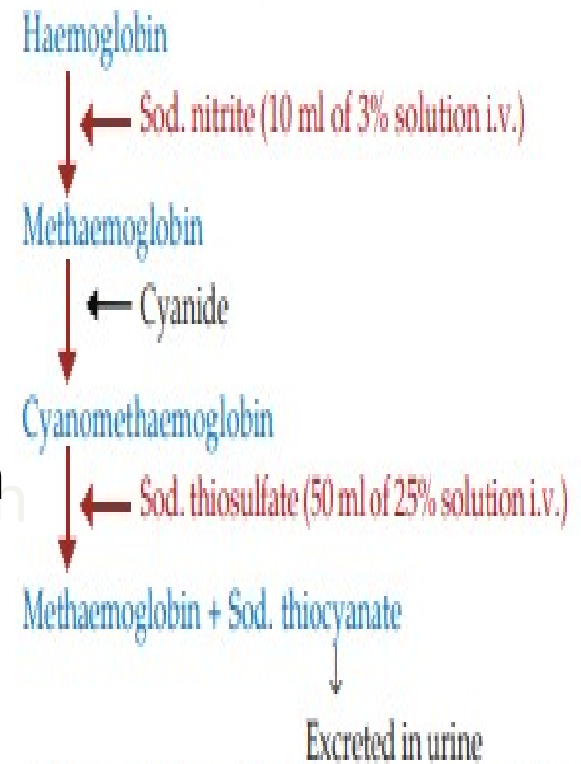
4- Biliary colic due to disease or morphine— responds to sublingual GTN or isosorbide dinitrate.

5- Esophageal spasm Sublingual GTN promptly relieves pain. Nitrates taken before a meal facilitate feeding in esophageal achalasia by reducing esophageal tone.

Therapeutic Uses of Nitrites

6-Cyanide poisoning

- Nitrites generate methaemoglobin which has high affinity for cyanide radical and forms cyanomethaemoglobin.
- BUT this may dissociate to release cyanide.
- Therefore, sodium thiosulfate is given to form Sod. thiocyanate which is poorly dissociable and is excreted in urine.



Sodium nitrite is used because it is a very weak vasodilator; large doses sufficient to generate enough methemoglobin can be injected i.v. without producing hypotension

Precautions:



① - 8-10 Hours nitrate-free period or alternate every 2 weeks to avoid tolerance with long acting nitrate.

② - Never Stop nitrate therapy ***Suddenly*** → Rebound ischemia & infarction.

③ - Do NOT take double dose. If a dose is missed → wait for the next dose.

④ Do Not use after expiry date → No effect.

⑤ - Not combined with ***Sildenafil*** (*Viagra*) →

Severe Hypotension → May be Fatal (also inhibit



Adverse Effects of Nitrates:

① - Postural hypotension & tachycardia Sit while taking it.

② - Tolerance & cross-tolerance between nitrites

& nitrates:

a- Due to depletion of S-H group required for denitration & activation

sustained treatment with nitroglycerin in vivo is associated with reduced biotransformation of nitrate to NO by endothelial mitochondrial enzyme

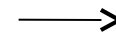
b- Avoid by daily 8-10 hours nitrate free or alternate *aldehyde dehydrogenase-2*,

with other Anti-anginal every 2 weeks

Adverse Effects of Nitrates:



- ③- Headache, Flush, dizziness & weakness
- ④- Met-Hb and cyanosis especially by Nitrites > Nitrates.
- ⑤- Hypersensitivity reaction as skin rash.
- ⑥- Hypotension : Reflex stimulation of Sympathetic system : Tachycardia : Short Diastolic Coronary perfusion blocked by B-Blockers or Verapamil (CCB)
- ⑥ Coronary Dependence after prolonged exposure to nitrates. Sudden stop of Nitrates □ Rebound coronary V.C. □ Ischemia & Infarction



Contraindications of Nitrates:

1. Allergy to nitrates
2. Heart rate is < 50 or > 100 beats/min.
3. Systolic BP is < 90 mm Hg
4. Concomitant use of phosphodiesterase (PDE) inhibitors such as tadalafil and sildenafil within the last 24 hours as they lead to **severe hypotension**
5. Right ventricular infarction. that the use of nitrates could significantly affect preload and, therefore, introduce hemodynamic instability
6. Hypertrophic cardiomyopathy. possible aggravation of the outflow tract obstruction
7. Increase intracranial pressure

1- Mention the mechanism of action of nitrates as antianginal drugs.

2-What are the preparations of nitrates used in different cases of angina?

SUGGESTED TEXTBOOKS



1. Whalen, K., Finkel, R., & Panavelil, T. A. (2018) Lippincott's Illustrated Reviews: Pharmacology (7th edition.). Philadelphia: Wolters Kluwer
2. Neal L. Benowitz, MD. In: Katzung BG (ed.). (2018). Basic & Clinical Pharmacology (14th edition) New York: McGraw-Hill Medical.

Cardiopulmonary module

Thank You